PCT/IN2004/000044

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING TRANSMITTAL OF COPY OF INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (CHAPTER I OF THE PATENT COOPERATION TREATY)
(PCT Rule 44bis.2(c))

Received with Thanks
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Date of mailing (day/month/year)	
31 August 2006 (31.08.2006)	
Applicant's or agent's file reference	IMPORTANT NOTICE
OP-CIT-JUB3	
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/IN2004/000044	16 February 2004 (16.02.2004)	
Applicant	JUBILANT ORGANOSYS LIMITED et al	

The International Bureau transmits herewith a copy of the international preliminary report on patentability (Chapter I of the Patent Cooperation Treaty)

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Form PCT/IB/326 (January 2004)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference CP-CIT-JUB3	FOR FURTHER ACTION	See item 4 below
International application No. PCT/IN2004/000044	International filing date *(day/month/year)* 16 February 2004 (16.02.2004)	Priority date *(day/month/year)*
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant JUBILANT ORGANOSYS LIMITED		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- [X] Box No. I — Basis of the report
- [ ] Box No. II — Priority
- [ ] Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- [X] Box No. IV — Lack of unity of invention
- [X] Box No. V — Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- [ ] Box No. VI — Certain documents cited
- [ ] Box No. VII — Certain defects in the international application
- [ ] Box No. VIII — Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis*.2).

	Date of issuance of this report 22 August 2006 (22.08.2006)
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Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IN2004/000044	16.02.2004	

International Patent Classification (IPC) or both national classification and IPC
C07D307/87

Applicant
JUBILANT ORGANOSYS LIMITED

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

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Box No. I Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☐ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☐ in written format

      ☐ in computer readable form

   c. time of filing/furnishing:

      ☐ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:

   ☒ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ not paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is

   ☐ complied with

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos.

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-15
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-15
Industrial applicability (IA)	Yes:	Claims	1-15
	No:	Claims	

2. Citations and explanations

   see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

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Reference is made to the following documents:

D1: WO 98/19511 (cited in the application)
D2: US 4 136 193 (cited in the application)
D3: US 4 650 884 (cited in the application)

Re Item IV

The International Searching Authority found multiple (groups of) inventions in this international application, the reasons being the following:

The present process according to claim 1 requires the following steps without isolation and purification of any intermediate stages:

a) subjecting 5-cyanophthalide to Grignard reaction with fluorophenyl magnesium bromide in a solvent medium
b) quenching said Grignard reaction mass with ammonium chloride solution, separating an aqueous layer and an organic layer containing cyanohydroxymethylketone, diluting said organic layer with alcoholic solvents and subjecting the resulting solution to a reduction reaction with sodium borohydride,
c) diluting the reaction mixture of step (b) with water, and then distilling off low boiling solvent and separating the water immiscible organic solvent
d) subjecting said water immiscible organic solvent containing dihydroxy compound to cyclisation reaction in the presence of catalytic amount of acid,
e) subjecting said cyclised product in a solvent to C-alkylation reaction with 3-N,N' dimethylaminopropyl chloride in the presence of a strong base to get citalopram.

The present process according to claim 10 requires the following steps without isolation of any intermediate stage:

a) subjecting 5-cyanophthalide to Grignard reaction with fluorophenyl magnesium bromide in a solvent medium
I) subjecting said Grignard reaction mass of step a) to a further Grignard reaction with 3-N-N' dimethylaminopropylmagnesium chloride
II) said Grignard reaction mass of step I) is quenched with aqueous ammonium chloride solution followed by work up to get dihydroxy product
III) said dihydroxy product is subjected to cyclisation in acidic medium to get

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citalopram.

Common to the said two processes according to the present application are the starting and end product, the step a) and the requirement that no intermediate stage is isolated.

However, all of these features common to both processes are known from D1 which discloses the preparation of citalopram from 5-cyanophthalide comprising the following steps (cf. example 1):

a) subjecting 5-cyanophthalide Grignard reaction with fluorophenyl magnesium bromide in *dry THF*
b) quenching said Grignard reaction mass with *ethanol* followed by the addition of sodium borohydride
c) removing 2/3 of the solvent in vacuo followed by the addition of water, extraction with EtOAc and isolation of crude (4- Cyano-2-hydroxymethylphenyl) (4-fluorophenyl)methanol
d) dissolving said crude intermediate in 60% H_3PO_4 for cyclisation and isolation of the intermediate
e) dissolving the intermediate from d) in DME followed by successive treatment with a mixture comprising nBuLi/diisopropylamine/DME and 3-dimethylaminopropylchloride to obtain citalopram.

On page 5 of the description (cf. line 28), D1 teaches that the process of the invention may be carried out with or without isolation of intermediates.

In view of the above mentioned process of D1 and the teaching in the description, the different processes according to present claims 1 and 10 do not share a common special technical feature as required by Rule 13.2 PCT. Therefore, the present application lacks unity of invention (Rule 13.1 PCT).

Re Item V

I Process according to claims 1-9.

1) Claim 1 is not clear because it does not comprise all essential features (Article 6 PCT).
In the description it is set out that one the major disadvantages of the prior art processes resides in the use of THF as solvent (cf. page 4, lines 1-3).

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Furthermore, it is taught that one of the major advantages of the present process is the use of a co-solvent as toluene/MDC with THF during the Grignard reaction (cf. page 8, lines 4-6). However, neither does the present claim 1 exclude the sole use of THF nor does it require the use of a co-solvent. Therefore, the claim 1 does not specify all of the essential features needed to define the invention.

2) The subject-matter of present claims 1-9 is new (Article 33(2) PCT; cf. below).

3) The subject-matter of claims 1-9 does not involve an inventive step (Article 33(3) PCT).

D1 represents the closest prior art and discloses the preparation of citalopram from 5-cyanophthalide comprising the following steps (cf. example 1):

a) subjecting 5-cyanophthalide to Grignard reaction with fluorophenyl magnesium bromide in *dry THF*
b) quenching said Grignard reaction mass with *ethanol* followed by the addition of sodium borohydride
c) removing 2/3 of the solvent in vacuo followed by the addition of water, extraction with EtOAc and isolation of crude (4-Cyano-2-hydroxymethylphenyl) (4-fluorophenyl)methanol
d) dissolving said crude intermediate in 60% H_3PO_4 for cyclisation and isolation of the intermediate
e) dissolving the intermediate from d) in DME followed by successive treatment with a mixture comprising nBuLi/diisopropylamine/DME and 3-dimethylaminopropylchloride to obtain citalopram.

On page 5 of the description (cf. line 28), D1 teaches that the process of the invention may be carried out with or without isolation of intermediates

The present process according to claim 1 differs from the process of D1 in that:

- in step b) the quenching is performed with ammonium chloride solution to give a two phase system followed by addition of alcoholic solvents to the organic phase
- In step c) the reaction mixture of step (b) is diluted with water followed by distilling off low boiling solvent and separating the water immiscible organic solvent whereas in D1 the sequence of the different process steps is different

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- in step d) the cyclisation reaction is carried out in the presence of catalytic amount of acid whereas in D1 excess acid is used.

The technical problem underlying the present application is seen in the provision of an alternative process for the preparation of citalopram.

The above mentioned modifications are merely straightforward alternatives from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.
For example, D1 teaches that in the cyclisation reaction (step d) p-toulenesulfonic acid can be used (cf. page 4, lines 24-27) which is usually applied in catalytic amounts. Furthermore, D2 discloses the Grignard reaction of 5-bromophthalide with fluorophenyl magnesium bromide followed by quenching with ammonium chloride solution (cf. example 1).

The dependent claims 2-9 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to novelty and/or inventive step.

II Process according to claims 10-15.

Re Item V

1) The subject-matter of present claims 10-15 is new (Article 33(2) PCT; cf. below).

2) The subject-matter of claims 10-15 does not involve an inventive step (Article 33(3) PCT).

D3 represents the closest prior art and discloses the preparation of citalopram from 5-cyanophthalide comprising the following steps (cf. examples 1 and 2):

a) subjecting 5-cyanophthalide to Grignard reaction with fluorophenyl magnesium bromide in a solvent medium
l) subjecting said Grignard reaction mass of step a) to a further Grignard reaction

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with 3-NN' dimethylaminopropylmagnesium chloride

ii) pouring said Grignard reaction mass of step I) into icewater followed by the addition of acetic acid and work up to give the dihydroxy product dissolved in toluene

iii) subjecting said dihydroxy product to cyclisation in acidic medium (sulfuric acid) to get citalopram.

In this process of D3 none of the intermediates is isolated (see also column 3, lines 10-19 of D3).

The present process according to claim 10 merely differs from the process of D1 in that in step ii) the quenching is performed with aqueous ammonium chloride solution instead of icewater/acetic acid.

The technical problem underlying the present application is seen in the provision of an alternative process for the preparation of citalopram.

The above mentioned modification is merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed.
In order to support this finding, D2 can be mentioned which discloses two successive Grignard reactions starting from 5-bromophthalide (cf. example 1). Both reaction mixtures are quenched with aqueous ammonium chloride solution.

Consequently, the subject-matter of the present claim 10 does not involve an inventive step.
The dependent claims 11-15 do not appear to contain any additional features which, in combination with the features of any claim to which they refer, meet the requirements of the EPC with respect to novelty and/or inventive step.